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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,955	07/11/2001	Gabriel Stavros Panayi	78104.023	2246

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EXAMINER
ROARK, JESSICA H

ART UNIT	PAPER NUMBER
1644	

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17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/806,955	Applicant(s) PANAYI ET AL.	
	Examiner Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2002 and 02 October 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,22-24,30,32-34 and 40-54* is/are pending in the application.

4a) Of the above claim(s) *30,32,34,40,41 and 43* is/are withdrawn from consideration.

5)☒ Claim(s) *18 and 54* is/are allowed.

6)☒ Claim(s) *22-24 and 44-53* is/are rejected.

7)☒ Claim(s) *33 and 42* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. The Examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Jessica Roark, Art Unit 1644, Technology Center 1600.

2. Applicant's amendments, filed 8/2/02 and 10/7/02 (Paper Nos. 12 and 15), are acknowledged.
Claims 19-21, 25-29, 31 and 35-39 have been cancelled. Claims 1-17 have been cancelled previously.
Claim 54 has been added.
Claims 18, 22-23, 30, 32-33, 40-44 and 46-53 have been amended.
Claims 18, 22-24, 30, 32-34 and 40-54 are pending.

3. Applicant's request, filed 8/2/02, for rejoinder of method claims including all limitation of allowable product claims is acknowledged.

Claims 18 and 54 are directed to an allowable product. Pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86), claims 33 and 42, directed to the process of making or using the patentable product, previously withdrawn from consideration as a result of a restriction requirement, are now subject to being rejoined. Process claims 33 and 42 hereby rejoined and fully examined for patentability under 37 CFR 1.104. In accordance with the Official Gazette notice, *supra*, process claims 30, 32, 34, 40-41 and 43, which do not depend from or otherwise include all the limitations of the allowable product, have NOT been rejoined.

Claims 30, 32, 34, 40-41 and 43 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in Paper No. 9.

Claims 18, 22-24, 33, 42 and 44-54 *are under consideration in the instant application.*

Sequence Compliance

4. Sequence compliance: The CRF, paper copy of the Sequence Listing and Statement that the CRF and Sequence Listing are identical, filed 10/2/02, has been found acceptable and entered.

Drawings

5. The formal drawings submitted 7/11/01 have been approved by the Draftsman.

Priority

6. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

IDS

7. Applicant's IDS, filed 4/6/01 (Paper No. 1.5), is again acknowledged.

Specification

8. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to the drawings, ***each of the lettered items should appear in upper case, without underling or bold type, as section headings***. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.
(b) Cross-Reference to Related Applications.
(c) Statement Regarding Federally Sponsored Research or Development.
(d) Reference to a "Sequence Listing," a table, or a computer program listing appendix submitted on compact disc (see 37 CFR 1.52(e)(5)).
(e) Background of the Invention.
    1. Field of the Invention.
    2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) Brief Summary of the Invention.
(g) Brief Description of the Several Views of the Drawing(s).
(h) Detailed Description of the Invention.
(i) Claim or Claims (commencing on a separate sheet).
(j) Abstract of the Disclosure (commencing on a separate sheet).
(k) Drawings.
(l) Sequence Listing, if on paper (see 37 CFR 1.821-1.825).

Applicant should amend the specification to provide the appropriate section headings.
In addition, the "Brief Description of the Drawings" should be moved to the appropriate location.

9. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

10. This Office Action will be in response to applicant's arguments, filed 8/2/02 (Paper No. 12). The rejections of record can be found in the previous Office Action (Paper No. 10).

It is noted that New Grounds of Rejection are set forth herein.

11. For examination purposes, the following is noted:

A) The phrase "having an amino acid sequence as shown in SEQ ID NO:1 or SEQ ID NO:2" is considered to require the full length of either SEQ ID NO:1 or SEQ ID NO:2 to be present; in addition it is considered to be "open" claim language, permitting the addition of an unspecified number of additional residues to the ends of either sequence.

B) SEQ ID NO:1 and SEQ ID NO:2 appear to differ only by the presence or absence of a 6-His tag.

Claim Objections

12. Claim 47 is objected to because of the following informalities: line 1 should read "comprising *an* immunoglobulin heavy chain". Appropriate correction is required.

13. Claims 49 and 52 are objected to because of the following informalities: the underlining should be removed from the article "a" in the first line of each claim. Appropriate correction is required.

14. Claims 33 and 42 are objected to as being dependent on a non-elected claim. Each of claims 33 and 42 should be written as an independent claim.

Claim Rejections - 35 USC § 112

15. The previous rejection of claims 18, 22-25 and 44-53 under 35 U.S.C. 112, first paragraph, scope of enablement is withdrawn in view of Applicant's amendment and arguments, filed 8/2/02, and the Declaration under 37 CFR 1.132 of Dr. Panayi, also filed 8/2/02.

It is acknowledged that BiP(GRP78) is an art-recognized designation for a particular member of the HSP70 *family* of proteins, and was recognized in the art to be distinct from the protein known in the art as Hsp70 (e.g. as reviewed by Hass, I.G., in Experientia 1994; 50(11-12):1012-1020; and by Munro and Pelham in Cell 1986; 46:291-300).

16. Claims 22-24 and 44-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated immunoglobulin heavy chain binding protein designated BiP(GRP78); does not reasonably provide enablement for "a fragment thereof" or pharmaceutical compositions and kits comprising "a fragment thereof". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The amended claim language is drawn to subsequences of any BiP(GRP78) polypeptide because it recites "or a fragment thereof".

Applicant has noted in the Remarks, filed 8/2/02, with respect to the amendment filed 8/2/02 to replace the "or a peptide derived therefrom" language that fragments of BiP(GRP78) would be expected to retain the function of the full length protein.

However, the specification does not appear to provide sufficient guidance such that the skilled artisan could practice the invention as broadly claimed. The specification discloses the polypeptides of SEQ ID NO:1 and SEQ ID NO:2. The specification also discloses and the 1.132 Declaration of Dr. Panayi filed 8/2/02 further supports, that these polypeptides can be used to inhibit the development of collagen-induced arthritis and that these polypeptide can be used to detect antibodies that correlate with the presence of rheumatoid arthritis in patients (e.g., pages 15-17).

However, the specification does not appear to provide sufficient guidance as to which subsequences of BiP(GRP78) proteins in general, or of SEQ ID NOS:1 or 2 in particular, the skilled artisan could use as disclosed for the full length proteins of SEQ ID NO:1, SEQ ID NO:2, and other full length art-recognized BiP(GRP78) proteins.

While the examiner acknowledges that the BiP(GRP78) polypeptides are highly conserved, as also set forth in the Declaration under 37 CFR 1.132 of Dr. Panayi, conservation among family members still does not provide sufficient guidance as to which *fragments* of a BiP(GRP78) polypeptide could be used as disclosed in the specification. Fragments of even a particular SEQ ID NO encompass an extremely large number of subsequences.

Applicant's comments, filed 8/2/02, regarding the retention of function for different proteins after truncation of residues is acknowledged. However, the instant claims are not drawn to defined truncations and instead encompass any subsequence of any BiP(GRP78) protein.

Neither does Applicant appear to have provided any working examples of any functional fragments of any particular BiP(GRP78) polypeptide. Thus it would require undue experimentation of the skilled artisan to determine which subsequences of SEQ ID NO:1would have the function of the full length molecule, and in turn identify nucleic acid subsequences of SEQ ID NO:2 which encode these subsequences.

Claim 24 is included in the rejection because although claim 24 limits the immunoglobulin heavy chain binding protein to an amino acid sequence as shown in SEQ ID NO:1 or SEQ ID NO:2, this recitation only further defines the immunoglobulin heavy chain binding protein of claim 22 and does not exclude the composition administered from including "a fragment thereof".

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the identity of which subsequences would encode a functional polypeptide is unpredictable; thus the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

17. The previous rejection of claims 18, 22-25 and 44-53 under 35 U.S.C. 112, first paragraph, written description, is withdrawn in view of Applicant's amendment and arguments, filed 8/2/02

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19. Applicant's amendment, filed 8/2/02 and limiting claim 18 to SEQ ID NO:1 or SEQ ID NO:2 has obviated the previous rejection of claim 18 under 35 U.S.C. 102(b) as being anticipated by
Ting et al. (DNA 1988; 7:275-286, IDS), or
Swiss-Prot Accession #P11021 (of record), or
Witzmann et al. (Fundamentals and Applied Toxicology 1994; 23(1):1-8, of record), or
Haas et al. (Proc. Natl. Acad. Sci. USA 1988; 85(7):2250-2254, of record), or
Hsu et al. (Protein Expression and Purification 1994; 5(6):595-603, of record), or
Kozutsumi et al. (J. Cell Sci. (supt) 1989; 11:115-137, of record).

20. Claims 22-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Kozutsumi et al. (J. Cell Sci. (supt) 1989; 11:115-137, of record).

Applicant's arguments, filed 8/2/02, have been fully considered but have not been found convincing.

Applicant acknowledges that intended use of a composition is not given patentable weight, but nevertheless argues that Kozutsumi et al. do not teach a pharmaceutical composition of BiP(GRP78) because no disease was treated with the composition of Kozutsumi et al. Applicant also argues that Kozutsumi et al. do not teach a pharmaceutical composition comprising an "anti-rheumatoid-arthritic amount" of BiP(GRP78).

Applicant further argues that Kozutsumi et al. teach a fusion protein comprising BiP(GRP78) rather than an isolated BiP(GRP78) protein.

However, Kozutsumi et al. teach cloning an immunoglobulin heavy chain binding protein designated BiP(GRP78) and placing a recombinant form of this protein in a pharmaceutical-suitable carrier (i.e. phosphate buffered saline and complete/incomplete Freund's adjuvant; see the entire document, page 118 in particular).

That the composition is then used to immunize rabbits is irrelevant because as acknowledged by Applicant and noted earlier, intended use of a composition does not carry patentable weight.

Applicant's inclusion of a limitation requiring an "anti-rheumatoid-arthritic amount" of BiP(GRP78) is acknowledged. However, Applicant provides no evidence that the 500μg of recombinant BiP(GRP78) formulated in the composition of Kozutsumi et al. would not be an "anti-rheumatoid-arthritic amount" of BiP(GRP78).

Finally, although the BiP(GRP78) protein of the composition of Kozutsumi et al. is a fusion protein, the fusion protein includes the full length sequence of BiP(GRP78) (see especially comments on page 118 "Expression of GRP78 in E. coli"). The claims do not exclude BiP(GRP78) in the form of a fusion protein; thus Applicant is arguing a limitation not claimed.

Therefore, the Examiner maintains that the teachings of Kozutsumi et al. anticipates the claimed invention.

21. Claims 44, 48 and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by McGuire et al., U.S. Patent 5,188,964, of record.

Applicant's arguments, filed 8/2/02 assert that independent claim 44 has been amended to recite SEQ ID NOS:1 and 2.

However, the amendment filed 8/2/02 does not incorporate these changes into independent claim 44 as asserted. Neither does the marked up copy of the claims filed 8/2/02 bear these changes.

The changes actually made to claim 44 in the amendment filed 8/2/02 do not appear to affect the rejection of record in Paper No. 10.

As previously noted:

> The '964 patent teaches heat shock proteins and a relationship between said heat shock proteins and glucose-related proteins (GRP's), and grp94 and grp78 are two major grp's (see column 2, lines 22-27 in particular). The '964 patent further teaches kits comprising Western Blot and ELISA assays comprising the immunoglobulin heavy chain binding proteins/stress-response proteins for detection and measurement of stress response proteins, such as grp94 (see claims 14-24 in particular).

Therefore, the rejection of record in Paper No. 10 is maintained with respect to the amended claims for the reasons of record.

Claim Rejections - 35 USC § 103

22. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

23. Claim 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over McGuire et al., U.S. Patent 5,188,964, of record.

Applicant's arguments, filed 8/2/02 assert that independent claim 44 has been amended to recite SEQ ID NOS:1 and 2.

However, the amendment filed 8/2/02 does not incorporate these changes into independent claim 44 as asserted. Neither does the marked up copy of the claims filed 8/2/02 bear these changes.

The changes actually made to claim 44 in the amendment filed 8/2/02 do not appear to affect the rejection of record in Paper No. 10.

As previously noted:

> The '964 patent has been discussed supra.
> The '964 patent does not teach instructions for the use of the kit.
>
> It would have been obvious to one of ordinary skill in the art at the time the invention was made to include instructions for the kit taught by the '964 patent for commercial use.
>
> One of ordinary skill in the art would have been motivated to provide instructions for persons outside of the producing library to ascertain how to use the kit as taught by the '964 patent.

Therefore, the rejection of record in Paper No. 10 is maintained for the reasons of record.

24. Claims 44, 45, 46, 49, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over McGuire et al., U.S. Patent 5,188,964, of record, in view of Hsu et al. (Protein Expression and Purification 1994; 5(6):595-603, of record), or Sambrook et al. (Molecular Cloning: A Laboratory Manual (1989) Cold Spring Harbor Laboratory Press, New York; page 17.2, of record).

Applicant's arguments, filed 8/2/02 assert that independent claim 44 has been amended to recite SEQ ID NOS:1 and 2.

However, the amendment filed 8/2/02 does not incorporate these changes into independent claim 44 as asserted. Neither does the marked up copy of the claims filed 8/2/02 bear these changes.

The changes actually made to claim 44 in the amendment filed 8/2/02 do not appear to affect the rejection of record in Paper No. 10.

As previously noted:

The '964 patent has been discussed supra.
The '964 patent does not teach recombinant immunoglobulin heavy chain binding proteins (grp).

Hsu et al. teach recombinant immunoglobulin heavy chain binding proteins (i.e. glucose-regulated protein, grp78) which are in the same family as hsp 70, both of which recognize exposed, extended regions of polypeptide containing a large number of hydrophobic residues (see page 595, the Abstract and right column, final paragraph, and page 596, first 8 lines in particular).

Sambrook et al. teach "methods for expressing large amounts of protein from a cloned gene (i.e. recombinant) introduced into *Escherichia coli* have proven invaluable in the purification, localization, and functional analysis of proteins" (see page 17.2, first 3 lines in particular). Further, high levels of protein are produced, purification is relatively easy, and proteins produced are biologically active (see entire document).

It would have been obvious to one of ordinary skill in the art at the time the invention was made that the recombinant grp's taught by Hsu et al. or the recombinant technology taught by Sambrook et al. could be substituted for the non-recombinant grp's taught by the '964 patent as Western and ELISA blots are generic and any protein (recombinant or otherwise) can be tested. Claim 45 is included because it would be obvious to include instructions for a commercial product to be sold commercially.

One of ordinary skill in the art would have been motivated to substitute the recombinant proteins taught by Hsu et al. and Sambrook et al. in the Western and ELISA blots taught by the '964 patent because the assays were used to detect and measure the recombinant proteins as taught by the '964 patent.

Therefore, the rejection of record in Paper No. 10 is maintained for the reasons of record.

25. Upon reconsideration and in view of Applicant's arguments, filed 8/2/02 noting that Hsp70 is a protein distinct from Bip(GRP78), the previous rejection of claims 22-23 under 35 U.S.C. 103(a) as being unpatentable over Berberian et al., U.S. Patent 5,348,945 (of record), in view of Hsu et al. (Protein Expression and Purification 1994; 5(6):595-603, of record) is withdrawn.

Conclusion

26. Claims 18 and 54 appear to be allowable as the prior art does not teach SEQ ID NO:1 or SEQ ID NO:2 or provide motivation to make the exact modifications that would result in precisely these amino acid sequences.

27. Claims 33 and 42 would appear to be allowable if rewritten in independent form.

28. This application contains claims 30, 32, 34, 40-41 and 43 drawn to an invention nonelected with traverse in Paper No. 9. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
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December 12, 2002

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